National Institute of Arthritis and Metabolic Diseases, which permitted purchase of the Unicam spectrophotometer and provided funds temporarily to pursue the research; they are also grateful for an NSF Undergraduate Research Participation award to I. D. R. They also thank Professor R. L. Cleland for the generous loan of a constant temperature water circulator, and D. J. Hupe for valuable discussions.

Amine Catalysis of Elimination from a β-Acetoxy Ketone. A Study of Catalysis *via* Iminium Ion Formation

Donald J. Hupe, Martha C. R. Kendall, and Thomas A. Spencer*

Contribution from the Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755. *Received June 2, 1971*

Abstract: A kinetic study of the elimination of acetic acid from 9-acetoxy-10-methyl-*cis*-decalone-2 (**1**) to form 10-methyl-$\Delta^{1,9}$-octalone-2 (**2**) in aqueous solution has been made using hydroxide ion, hydronium ion, acetate ion, and a variety of amines as catalysts. General base catalysis is observed, defining distinct Brønsted lines with $\beta \cong 0.6$ for primary, secondary, and tertiary amines. A mechanism for this elimination reaction involving rate-determining proton abstraction is confirmed by observation of a large primary kinetic isotope effect when the elimination is performed on **1** appropriately labeled with deuterium. With primary amines having $pK_a < 8$, covalent catalysis by amines is also found, involving terms proportional to protonated amine and proportional to protonated amine times free amine. The bell-shaped pH–rate profiles observed as a consequence of the latter term have been completely analyzed into the component general base and covalent catalysis terms. All evidence, including a primary kinetic isotope effect, is consistent with rate-limiting abstraction of an α-proton from an iminium ion by a general base in the bimolecular covalent catalysis. A Brønsted β of $\sim$0.5 has been determined for this proton abstraction. Temperature-dependence studies indicate that the bimolecular catalysis has a large negative $\Delta S^{\pm}$ (−35 eu), but a relatively small $\Delta H^{\pm}$ (10 kcal/mol). It is estimated that conversion of a carbonyl compound to a cyanomethyliminium ion increases the rate of α-proton abstraction by a given general base by $\sim 10^6$. This nucleophilic catalysis is discussed as a model for certain enzymic processes and compared with previous related studies. Evidence is presented which is inconsistent with previously postulated analogous catalysis involving iminium ion formation by imidazole.

Despite several recent studies[1-6] of amine catalysis of carbonyl compound reactions, there still remain many incompletely understood aspects of this biologically important[7] type of process, particularly with respect to the details of covalent catalysis *via* iminium ion formation by primary and secondary amines. In the preceding paper,[8] a study of general base catalysis by amines of the elimination of hydrogen chloride from 9-fluorenylmethyl chloride was made in order to establish a background against which to search for catalysis involving amines as nucleophiles. In this paper, amine-catalyzed elimination of acetic acid from 9-acetoxy-10-methyl-*cis*-decalone-2 (**1**) has been investigated and has, as hoped, provided an opportunity to evaluate and study catalysis involving amine-carbonyl condensation.

Proposals of such covalent catalysis by amines, which were first advanced for the decarboxylation of β-keto acids[9] and the dealdolization of diacetone alcohol,[10] have been extended, with impressive if sometimes ambiguous[1] evidence, to aldehyde and ketone enolization in model systems,[2,4] and to reactions catalyzed by aldolases[11] and decarboxylases.[12] Of particular relevance to the β-elimination reaction studied in the present research are Abeles' investigation of the enzymic conversion of 2-keto-3-deoxy-L-arabonate to α-ketoglutarates emialdehyde,[13] Fedor's studies of general base catalyzed β-eliminations in model systems very similar to ours,[5] and Hine's recent finding of intramolecular bifunctional catalysis involving iminium ion formation.[4]

The particular β-acetoxy ketone (**1**) chosen as a substrate for the study described herein, while less readily prepared than other possibilities, has the distinct advantage of undergoing elimination essentially quantitatively to the chromophoric and stable enone **2**. It was also chosen because it is the same type of substance we have previously used to study the stereochemistry and mechanism of intramolecular aldol condensations[14] and ketol dehydrations.[15] The catalysts employed were

(1) L. P. Koshechkina, E. A. Shilov, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **35**, 55 (1969), and previous papers in this series.
(2) M. L. Bender and A. Williams, *J. Amer. Chem. Soc.*, **88**, 2502 (1966).
(3) G. E. Lienhard and T-C. Wang, *ibid.*, **90**, 3781 (1968).
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(5) L. R. Fedor and W. R. Glave, *ibid.*, **93**, 985 (1971), and previous papers in this series.
(6) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).
(7) See W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, especially Chapters 2 and 3 for a review and specific references.
(8) T. A. Spencer, M. C. R. Kendall, and I. D. Reingold, *J. Amer. Chem. Soc.*, **94**, 1250 (1972).
(9) K. J. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).
(10) F. H. Westheimer, *Ann. N. Y. Acad. Sci.*, **39**, 401 (1940).
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(12) F. H. Westheimer, *Proc. Chem. Soc.*, 253 (1963).
(13) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, **242**, 2751 (1967).
(14) T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 3785 (1963); T. A. Spencer, H. S. Neel, D. C. Ward, and K. L. Williamson, *J. Org. Chem.*, **31**, 434 (1966).

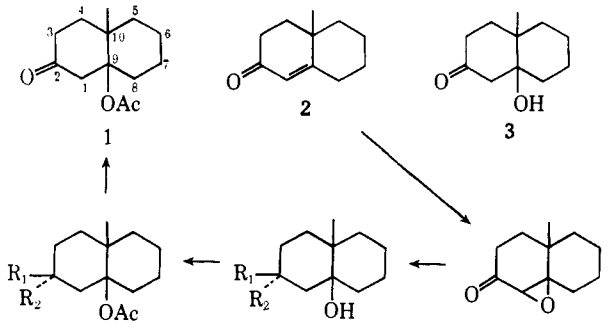
those used in the preceding paper,[8] augmented by additional amines suggested by the results as the study proceeded.

Results

Preparation of the desired β-acetoxy ketone **1** was initially attempted by direct acetylation of the readily available ketol **3**,[16] with, for example, isopropenyl acetate. Ir and nmr spectra of the acetylation products indicated that the material was largely **1**, but the acetoxy ketone would not crystallize and could not be purified by chromatographic or other methods, all of which caused an increase in the amount of enone **2** in the product.

Therefore, the indirect method shown in Scheme I (which was necessary in any case for the preparation of deuterated **1** as discussed below) was adopted.

Scheme I



7, R_1 = OAc; R_2 = H
8, R_1 = H; R_2 = OAc
9, R_1 = OH; R_2 = H
10, R_1 = H; R_2 = OH
5, R_1 = OH; R_2 = H
6, R_1 = H; R_2 = OH

Enone **2** was converted to the crystalline β-oxide **4** by the procedure of Kuehne and Nelson.[17] Hydride reduction of **4** afforded a mixture of the known[18] diols **5** and **6** epimeric at C_2, and acetylation with isopropenyl acetate converted these to a mixture of the corresponding diacetates **7** and **8**[18] in 33% overall yield from **2**. Selective hydrolysis of the secondary acetate groups of **7** and **8** with methanolic sodium hydroxide at 25° afforded a mixture of hydroxyacetates **9** and **10**, which were purified by preparative tlc (54% yield) and oxidized with Jones reagent[19] to the desired **1** (88% yield), which could thus be obtained crystalline and pure, mp 49–50°.

In order to determine whether the conversion of **1** to **2** would show a kinetic isotope effect, ketoacetate **1** substituted at C_1 with deuterium was also required as a substrate. This was prepared by a completely analogous route starting with pentadeuterio enone **2** (**2**-d_5) prepared by exhaustive isotopic exchange of **2** in deuteriomethanol–sodium methoxide. Deuterium incorporation was followed to completion by disappearance of the vinyl proton peak in the nmr spectrum of **2**. No loss of deuterium at C_1 was detectable after the basic epoxidation of **2**-d_5. Subsequent reduction with lithium aluminium deuteride, acetylation, and selective

(15) T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Lett.*, 3889 (1965).
(16) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
(17) M. E. Kuehne and J. A. Nelson, *ibid.*, **35**, 161 (1970).
(18) H. B. Henbest and J. McEntee, *J. Chem. Soc.*, 4478 (1961).
(19) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

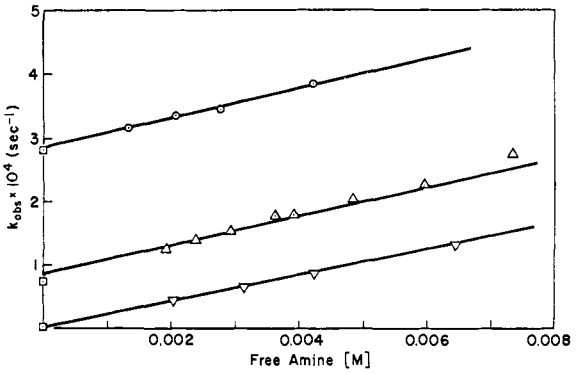


Figure 1. Plot of pseudo-first-order rate constants, k_{obsd}, for the reaction of **1** to give **2** *vs.* concentration of free 1,4-diazabicyclo-[2.2.2]octane (DABCO) at pH 10.37 (○), pH 9.77 (△), and pH 7.89 (▽). The intercepts (□) are calculated values of $k_{OH}[OH^-]$ at the respective pH values. ($k_H[H_3O^+]$ is negligible at these pH values.)

hydrolysis all were conducted exactly as with the unlabeled analogs. The final Jones oxidation to **1**-C_1-d_2 required more vigorous reaction conditions, however, presumably owing to the primary kinetic isotope effect caused by the C_2 deuterium atom.[20] The nmr spectrum of the product ketoacetate confirmed that it was essentially completely deuterated at C_1, for none of the usually readily discernible AB quartet for the C_1 protons at δ 3.1 ppm could be detected.

The reaction of dilute solutions of **1** (and later **1**-C_1-d_2) in water was monitored by observing the increase in ultraviolet absorption at 247 mμ caused by formation of **2**. As anticipated, the reaction proceeded essentially quantitatively and afforded excellent pseudo-first-order kinetics under almost all catalytic circumstances.

The rate of formation of **2** from **1** is described by eq 1

$$\frac{d[2]}{dt} = \{k_H[H_3O^+] + k_{OH}[OH^-] + \sum_i k_B^i[B^i] + k_A[RNH_3^+] + \sum_i k_{AB}^i[RNH_3^+][B^i]\}[1] \quad (1)$$

where $[H_3O^+]$ is a_H as measured by pH meter, $[OH^-]$ is K_w/a_H, RNH_3^+ is a protonated primary amine, and B is any general base present. The value of k_H was obtained from the slope of a plot of k_{obsd} *vs.* a_H, in unbuffered hydrochloric acid solutions at pH < 2. Similarly, k_{OH} was determined as the slope of k_{obsd} *vs.* K_w/a_H for unbuffered runs at pH > 9. A pH-independent component ascribable to water catalysis was not detected.

Catalysis proportional to base concentration was observed with acetate buffer and every amine buffer examined. The value of the second-order rate constant for this general base catalysis, k_B, was determined from the slope of a plot of k_{obsd} *vs.* the concentration of free amine or acetate ion. The concentration of the general base, [B], was calculated by multiplying the total buffer concentration by $K_a/(K_a + a_H)$, where K_a is the ionization constant of the protonated species. For all tertiary amines, plots of k_{obsd} *vs.* [B] gave straight lines of slope k_B and intercept $k_H[H_3O^+] + k_{OH}[OH^-]$, as illustrated in Figure 1. Since no increase in the slope of the plots was found in any case for runs at pH values well below the pK_a, catalysis proportional to protonated

(20) F. H. Westheimer and N. Nicolaides, *J. Amer. Chem. Soc.*, 71, 25 (1949).

Table I. Rate Constants for the Reaction of **1** to Form **2** in Water at 25°

Catalyst	pK_a	k_{OH}, k_{H^+}, or k_B (M^{-1} sec^{-1})	pH range	Total catalyst concn [M]	No. of runs
Hydroxide ion	15.7	1.2	9.1–11.5	1.2×10^{-5}–3×10^{-3}	52
Hydronium ion	−1.7	8.0×10^{-5}	1.3–1.8	1.6×10^{-2}–5×10^{-2}	4
Pyrrolidine	11.32[a]	3.1×10^{-1}	7.6–10.7	0.52–0.006	32
Piperidine	11.22[b]	1.3×10^{-1}	7.3–10.9	0.50–0.006	36
Hexamethylenimine	11.10[a]	1.9×10^{-1}	10.0–10.8	0.44–0.005	20
Quinuclidine	10.95[c]	2.2×10^{-1}	7.4–10.8	0.59–0.01	28
Triethylamine	10.75[d]	2.5×10^{-3}	10.1–10.8	0.10–0.006	16
N-Butylamine	10.61[d]	3.2×10^{-2}	10.4–11.1	0.40–0.005	20
N-Methylpiperidine	10.19[c]	2.0×10^{-3}	7.3–8.8	0.03–0.002	8
Piperazine	9.82[e]	3.0×10^{-2}	9.2–9.3	0.37–0.005	12
Trimethylamine	9.76[b]	4.6×10^{-2}	8.5–9.7	0.43–0.006	28
Allylamine	9.49[b]	5.9×10^{-3}	8.8–9.4	0.53–0.007	20
Ethoxyethylamine	9.44[f]	5.2×10^{-3}	8.5–9.6	0.40–0.005	20
1,4-Diazabicyclo[2.2.2]octane	8.70[g]	2.2×10^{-2}	7.9–8.6	0.04–0.01	36
Morpholine	8.36[a]	3.5×10^{-3}	7.8–8.9	0.25–0.003	36
Ethyl glycinate	7.73[h]	6.7×10^{-4}	5.7–7.7	0.50–0.007	28
N-Methylmorpholine	7.41[b]	1.2×10^{-4}	6.5–7.4	0.38–0.005	16
N-Methylimidazole	7.06[i]	8.9×10^{-4}	6.6–7.2	0.14–0.009	12
Imidazole	6.95[j]	8.9×10^{-4}	6.7–7.2	0.60–0.008	16
2,2,2-Trifluoroethylamine	5.70[k]	3.6×10^{-5}	2.9–7.1	0.38–0.02	24
Cyanomethylamine	5.34[l]	3.8×10^{-5}	2.9–7.1	0.43–0.005	40
Acetate ion	4.76[m]	1.2×10^{-5}	4.2–5.0	0.38–0.02	12
N,*N*-Dimethylcyanomethylamine	4.20[n]	5.7×10^{-6}	4.2–5.0	0.38–0.02	12

[a] H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956). [b] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957). [c] C. A. Grob, A. Kaiser, and E. Renk, *Chem. Ind. (London)*, 598 (1957). [d] N. A. Lange, "Handbook of Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, pp 1203–1204. [e] J. Bjerrum, "Stability Constants," Chemical Society, London, 1958, Part I, p 21. [f] R. C. Cavestri and L. R. Fedor, *J. Amer. Chem. Soc.*, **92**, 4610 (1970). [g] The Merck Index, 8th ed, Merck & Co., Inc., Rahway, N. J., 1968, p 1072. [h] O. H. Emerson and P. L. Kirk, *J. Biol. Chem.*, **87**, 597 (1930). [i] Determined in this study by the half-neutralization method. [j] T. C. Bruice and G. L. Schmit, *J. Amer. Chem. Soc.*, **80**, 148 (1958). [k] E. R. Bissel and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959). [l] G. W. Stevenson and D. Williamson, *J. Amer. Chem. Soc.*, **80**, 5943 (1958). [m] Reference 3. [n] S. Soloway and A. Lipschitz, *J. Org. Chem.*, **23**, 613 (1958).

tertiary amine is unimportant. For primary and secondary amines with $pK_a > 9$, k_B could be obtained as for tertiary amines. For primary amines of low pK_a, however, it was necessary to obtain k_B from runs done at pH values well above the pK_a in order to minimize other kinetic terms discussed below.[21] All the second-order rate constants, k_B, are summarized in Table I. A Brønsted plot of log k_B *vs.* pK_a is shown in Figure 2. The rationale for drawing three lines of slope $\beta = 0.59$ is discussed below.

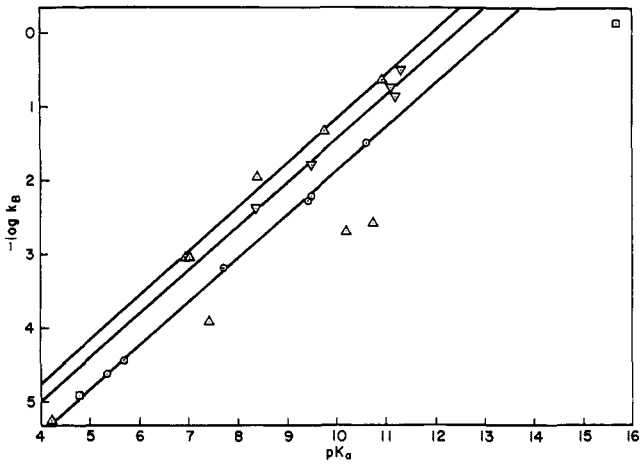


Figure 2. Brønsted plot of the logarithms of the second-order rate constants from Table I for the reaction of primary (○), secondary (▽), and tertiary (△) amines, and hydroxide ion and acetate ion (□), with **1** to give **2** *vs.* pK_a's of their conjugate acids. The slope of the lines is $\beta = 0.59$. (The points for the diamines piperazine and DABCO have been corrected according to the relationship given by Jencks, ref 7, p 173.)

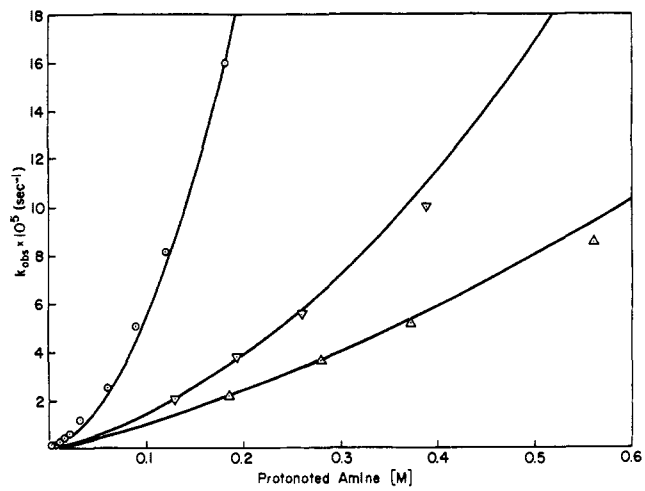


Figure 3. Plot of pseudo-first-order rate constants, k_{obsd}, for the conversion of **1** to **2** *vs.* concentration of protonated cyanomethylamine. Experimental points are given for runs at pH 3.81 (△), pH 4.40 (▽), and pH 5.35 (○). The curves at each pH were calculated from the expression $k_{obsd} = k_B[RNH_2] + k_A[RNH_3^+] + k_{AB}[RNH_2][RNH_3^+]$ using the appropriate rate constants from Table II.

The three primary amines with $pK_a < 8$, cyanomethylamine (CMA), 2,2,2-trifluoroethylamine (TFE), and

(21) Morpholine, the only secondary amine studied with $pK_a < 9$, was the one amine among all those used which gave anomalous kinetic behavior. Plots of k_{obsd} *vs.* [B] for morpholine had an as yet unexplained slightly *increasing* slope with increasing pH. (Morpholine might instead have been expected to show the opposite trend, exhibiting catalysis proportional to protonated amine analogous to that found for primary amines of slightly lower pK_a). The value of k_B for morpholine listed in Table I is therefore somewhat uncertain.

Table II. Values of k_B, k_A, and k_{AB} Obtained for Primary Amines with $pK_a < 8$

Amine	pK_a	k_A (M^{-1} sec^{-1})	k_B (M^{-1} sec^{-1})	k_{AB} (M^{-2} sec^{-1})
Cyanoethylamine (CMA)	5.34	1.0×10^{-4}	3.8×10^{-5}	4.1×10^{-3}
2,2,2-Trifluoroethylamine (TFE)	5.70	4.6×10^{-5}	3.6×10^{-5}	1.8×10^{-3}
Ethyl glycinate (EG)	7.73	3×10^{-6}	6.7×10^{-4}	4.0×10^{-3}

ethyl glycinate (EG), exhibited, in addition to the general base term, a term proportional to protonated amine concentration and a third-order term proportional to free amine times protonated amine concentrations. The latter term is responsible for the upward curvature seen in the plot of k_{obsd} *vs.* $[RNH_3^+]$ for CMA in Figure

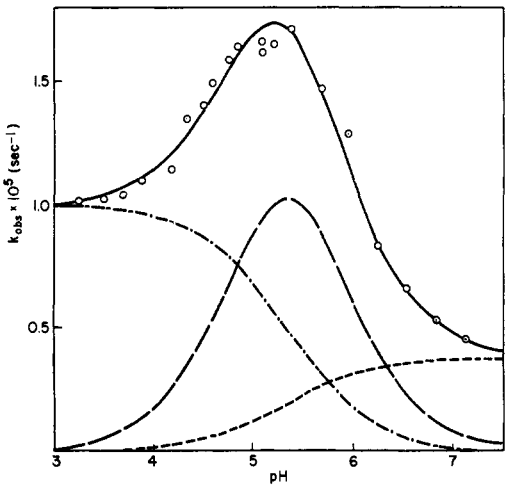


Figure 4. Plot of pseudo-first-order rate constants, k_{obsd}, for the conversion of **1** to **2** in the presence of 0.1 *M* total cyanomethylamine buffer *vs.* pH. The experimental points (○) are shown, as are curves for the $k_B[RNH_2]$ term (– – – –), the $k_A[RNH_3^+]$ term (–·–·–), the $k_{AB}[RNH_2][RNH_3^+]$ term (— — —), and their sum (——) calculated using the appropriate rate constants from Table II.

3. The rate constants for the protonated amine term, k_A, were obtained, at pH values well below the pK_a, from the slope of k_{obsd} *vs.* $[RNH_3^+]$, and are listed in Table II. The rate constants for the term proportional to free times protonated amine, k_{AB}, were obtained from values of k_{obsd} near the pK_a (where $k_H[H_3O^+]$ and $k_{OH}[OH^-]$ are negligible) by use of the expression $k_{AB} = (k_{obsd} - k_B[B] - k_A[RNH_3^+])/([RNH_3^+][RNH_2])$, and are also listed in Table II. From the appropriate rate constants the value for each of the kinetic terms for a 0.1 *M* total cyanomethylamine concentration was evaluated and is plotted as a function of pH in Figure 4. Their sum gives a good fit, as shown, with the experimentally determined points obtained under these conditions.

When a pH–rate profile was measured for CMA with a known amount of general base added (such as a tertiary amine or acetate ion), it was found that in addition to the terms delineated in Figure 4 for CMA and the k_B term for the added base, there was also a $k_{AB}[HCMA^+][B]$ term, where [B] is the concentration of free general base added. The latter term can dominate the catalysis as shown in Figure 5 for the case of 0.1 *M* CMA plus 0.5 *M* acetate ion. The lower curve is the computed sum of the k_A, k_B, and k_{AB} terms for CMA plus the k_B term for acetate ion. To this must be added

Table III. Third-Order Rate Constants, k_{AB}, from the Term $k_{AB}[RNH_3^+][B]$, Where B Is Water, Hydroxide Ion, or a General Base and RNH_3^+ Is Protonated Cyanomethylamine

Base (B)	pK_a	k_{AB} (M^{-2} sec^{-1})
H_2O	−1.7	1.8×10^{-6} [a]
DCMA	4.15	1.7×10^{-4}
OAc^-	4.76	1.8×10^{-2}
CMA	5.34	4.1×10^{-3}
Imidazole	6.95	1.0×10^{-1}
OH^-	15.7	$\sim 10^4$ [b]

[a] Obtained by dividing k_A by $[H_2O] = 55$ *M*. [b] None observed; this is an upper limit estimated as discussed in the text.

$1.8 \times 10^{-2}[HCMA^+][OAc^-]$ in order to obtain the upper curve which fits the experimental points. Similar additional k_{AB} terms have been found where the general base is dimethylcyanomethylamine (DCMA) or imidazole and have been included in Table III.

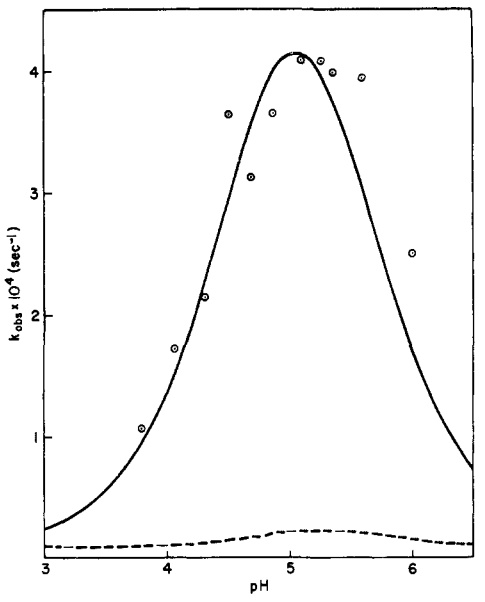


Figure 5. Plot of pseudo-first-order rate constants, k_{obsd}, for the conversion of **1** to **2** in the presence of 0.1 *M* cyanomethylamine buffer plus 0.5 *M* acetic acid buffer *vs.* pH. The experimental points (○) are shown, as are the curves, calculated using the appropriate rate constants from Tables II and III, for the total catalysis by this mixture (———), and for the catalysis by the two component buffer solutions acting independently (– – – – –).

The reaction of isotopically labeled keto acetate (**1**-C_1-d_2) with either hydroxide ion or trimethylamine exhibits a large kinetic isotope effect as indicated in Table IV. In both cases the pseudo-first-order plots for which k_{obsd} values were obtained were linear for several half-lives. The value of k_{AB} for the reaction of **1**-C_1-d_2 with CMA was obtained in the same manner as for **1**. A large isotope effect was again observed and the pseudo-first-order plot was linear for at least one half-life.

Table IV. Deuterium Isotope Effects Found for Rate Constants of Three Types for the Conversion of **1** to **2**

Catalyst	k	**1**	**1**-C_1-d_2	k^H/k^D
OH^-	k_{OH}	1.2	1.3×10^{-1}	9.2
$(CH_3)_3N$	k_B	4.6×10^{-2}	4.7×10^{-3}	9.8
CMA	k_{AB}	4.1×10^{-3}	6.5×10^{-4}	6.3

Temperature dependence studies were performed to obtain data for three kinetic terms: $k_{OH}[OH]^-$, $k_B[(CH_3)_3N]$, and $k_{AB}[CMA][HCMA^+]$. Measurements were made at 20, 25, 30, and 35°, and linear plots on ln k *vs.* $1/T$ (°K) with slope $-E_a/R$ were obtained in each case. The calculated activation parameters are given in Table V.

Table V. Activation Parameters Calculated[a] for Three Kinetic Terms for the Conversion of **1** to **2**

Term	E_a (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
$k_{OH}[OH^-]$	18.5	17.9	17.4	2
$k_B[(CH_3)_3N]$	17.4	16.8	19.4	−9
$k_{AB}[HCMA^+][CMA]$	10.8	10.2	20.7	−35

[a] Calculated from $\Delta H^{\ddagger} = E_a - RT$; $\Delta G^{\ddagger} = -2.303\,RT \log (k_2h/kT)$; $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$.

Discussion

As indicated in eq 1 the rate of formation of **2** from **1** in aqueous solution has terms proportional to the concentrations of hydronium ion, hydroxide ion, and any general base, B, in solution. The hydronium ion catalysis will not be considered in this paper. Similar general base catalysis of elimination of acetic acid from a β-acetoxy ketone has been studied by Fedor,[5] who concluded that α-proton abstraction is the rate-determining step and that loss of acetate from the intermediate carbanion is fast compared to re-formation of starting material. The data obtained for loss of acetic acid from **1** and **1**-C_1-d_2 are entirely consistent with such a mechanism, where formation of $\mathbf{1}^-$ is the slow step,[22] with $k_2 \gg k_{-1}$ in eq 2.[23] An ElcB mechanism, in which

$$\mathbf{1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{1}^- \xrightarrow{k_2} \mathbf{2} \qquad (2)$$

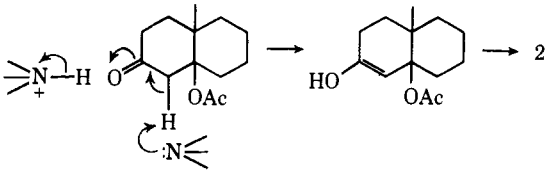
a rapid equilibrium is established between **1** and $\mathbf{1}^-$, with slow decomposition of $\mathbf{1}^-$ to **2**, can be ruled out because specific, not general, base catalysis should be observed in that case.[5] As discussed in the preceding paper, we can also rule out the kinetically equivalent mechanism involving ammonium ion catalyzed conversion of $\mathbf{1}^-$ to **2** as the rate-limiting step on the basis of the observation of a large, undiminishing, primary kinetic isotope effect with **1**-C_1-d_2.

The Brønsted plot (Figure 2) for these k_B terms is analogous to that obtained in our prefatory study of the dehydrohalogenation of 9-fluorenylmethyl chloride,[8] for which rate-determining proton abstraction by general bases was also postulated. Recognition that the data from the elimination of **1** could most reasonably be represented as three distinct Brønsted lines for primary, secondary, and tertiary amines, rather than as one Brønsted line (as has been done for closely related reactions[2]), depended, in fact, on the availability of the results from the 9-fluorenylmethyl chloride case. The reasons for the existence of different Brønsted lines for different classes of amines were reviewed in the preceding paper.[8]

Steric hindrance is reflected in the relatively ineffective general base behavior of several of the tertiary amines studied (Figure 2), consistent with previous observations.[24-27] Hydroxide ion also shows a precedented[27,28] negative deviation from the Brønsted plot. It is worth noting that imidazole and *N*-methylimidazole behave as essentially unhindered general bases with k_B's falling close to the Brønsted line when acting as catalysts for proton abstraction from C_1 of **1**, in contrast to their apparently anomalous ineffectiveness in the preceding study.[8]

For certain primary amines, the conversion of **1** to **2** involves, in addition to general base catalysis, kinetic terms proportional to protonated amine concentration ($k_A[RNH_3^+]$) and protonated amine concentration times free amine concentration ($k_{AB}[RNH_3^+][B]$), as delineated in eq 1. For reasons discussed below, these terms are ascribed to catalysis involving imine formation between the amine and **1**. Although perhaps the simplest transition state representation of the bimolecular catalysis of **1** → **2** would be concerted general base–general acid catalysis of enolization as shown in Scheme II,

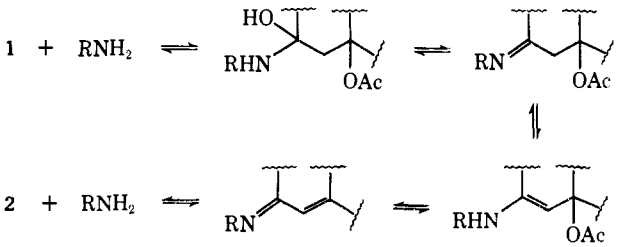
Scheme II



such processes are usually not observed in aqueous solution[29] and there is no reason why unhindered tertiary amines should not be as effective in such a mechanism as comparably basic primary amines.

In Scheme III are shown the steps (except proton transfers between oxygen and nitrogen) which must be

Scheme III



(22) The species designated $\mathbf{1}^-$ refers to the C_1-enolate ion from **1**. Clearly the possibility exists for formation of the alternate C_3-enolate ion, and there is evidence (see the Experimental Section) that isotopic exchange at C_3 does occur competitively with the formation of **2**.

(23) As in the previous paper,[8] we are not considering the subtle question of whether departure of acetate ion may be essentially simultaneous with the rate-limiting proton abstraction, and are assuming the discrete existence of intermediate enolate ions and, as discussed later, enamines.

(24) J. Weinstock, R. G. Pearson, and F. G. Bordwell, *J. Amer. Chem. Soc.*, **78**, 3473 (1956).

(25) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *ibid.*, **87**, 5050 (1965).

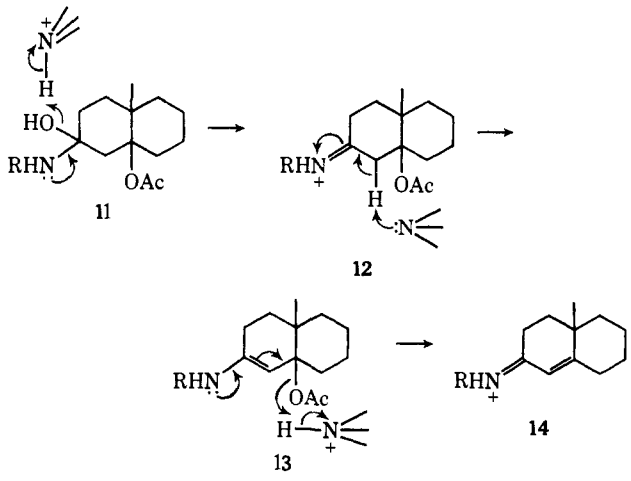
(26) C. D. Gutsche, D. Redmore, R. S. Buriks, K. Nowotny, H. Grassner, and C. W. Armbruster, *ibid.*, **89**, 1235 (1967), and references therein.

(27) L. R. Fedor, *ibid.*, **89**, 4479 (1967).

(28) J. Hine, K. G. Hampton, and B. C. Menon, *ibid.*, **89**, 2664 (1967).

(29) See reference 7, pp 201–202, for a discussion of this point and references.

involved in covalent catalysis by a primary amine of an elimination reaction such as **1** → **2**. There are clearly several potential rate-determining steps which, *a priori*, could involve bimolecular catalysis of the type observed. For example, the kinetically equivalent rate-limiting steps **11** → **12**, **12** → **13**, and **13** → **14** could be envisaged.



Rate-determining iminium ion formation, as in **11** → **12**, seemed improbable on the basis of the known rates of imine ⇄ carbonyl interconversion in similar systems, which are much faster than the rate of formation of **2** from **1**.[30,31] Rate-determining general acid catalyzed loss of acetate from an enamine, as in **13** → **14**, likewise seemed very improbable in view of our observation[32] that similar bimolecular catalysis of the dehydration of ketol **3** has very nearly the same rate constant, despite the large difference in leaving group capacity between acetate and hydroxide ions.

The expectation that general base catalyzed proton abstraction from an intermediate iminium ion, as in **12** → **13**, was the rate-limiting step in the overall process was conclusively confirmed by the kinetic studies using **1**-C_1-d_2, which showed a large kinetic isotope effect in the k_{AB} term (Table IV), indicating that a C_1–D bond was partially broken in the transition state. If the rate-limiting step were **13** → **14**, one would expect isotopic exchange at C_1 to occur in equilibrium steps prior to the formation of **14**, so that a primary isotope effect would be observed only at the beginning of the reaction, if at all.

The catalysis proportional to protonated amine concentration observed with low-pK_a primary amines (k_A term) is best explained by a mechanism analogous to that postulated for the k_{AB} terms with water acting as the base for proton abstraction from the iminium ion. The lack of such catalysis by protonated tertiary amines indicates that it is not general acid catalysis of enolization of **1**.

In order to facilitate visualization of how the k_B, k_A, and k_{AB} terms vary with change in the pK_a of the primary amine catalyst, pH–rate profiles for 0.5 *M* total amine concentrations of CMA, TFE, and EG were calculated using the rate constants in Table II, and are plotted in Figure 6. The plateau above the

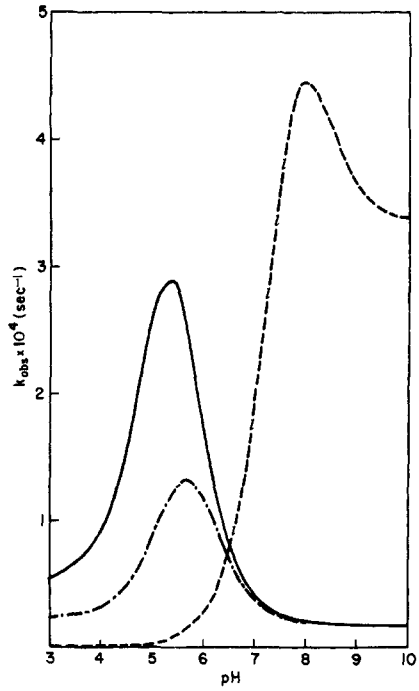


Figure 6. Plot of values of k_{obsd}, calculated using the appropriate rate constants from Table II, for the conversion of **1** to **2** as catalyzed by 0.5 *M* total buffer concentrations of CMA (——), TFE (-·-·-), and EG (– – – –) *vs.* pH.

pK_a for each amine reflects the k_B term which increases with increasing pK_a of the amine. The plateau below the pK_a for the primary amines reflects the k_A term. The magnitude of this k_A term depends on both the equilibrium concentration of iminium ion **12** and the ease with which the proton is abstracted from **12** by water. The concentration of iminium ion would be expected to increase slightly as the pK_a of the amine catalyst increases, on the basis of Hine's finding[33] of a small increase in equilibrium constant for imine formation with increasing pK_a and the assumption[2,34] that $pK_a^{amine} - pK_a^{imine} \cong 3$ irrespective of pK_a. On the other hand, iminium ions formed from amines with higher pK_a's should be less susceptible to conversion to the corresponding enamines **13** by α-proton abstraction. The fact that the k_A term decreases as the pK_a of the catalyst increases, as demonstrated in Table II and Figure 6, suggests that the latter factor is more important.

The k_{AB} terms, however, do not change markedly or regularly with increasing catalyst pK_a; the bell-shaped portions of the curves in Figure 6 are relatively constant in magnitude. Presumably the above effect which accounts for the decrease in rate with higher-pK_a amines in the k_A term is approximately balanced in the k_{AB} term by more effective proton abstraction as the strength of the general base increases. The fact that TFE has a k_{AB} about half as large as those for CMA or EG is consistent with the observation[33] that primary amines with sp^3-hybridized carbon atoms β to nitrogen have somewhat smaller equilibrium con-

(30) A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2508 (1966).

(31) (a) J. Hine, F. A. Via, J. K. Gotkis, and J. C. Craig, Jr., *ibid.*, **92**, 5186 (1970); (b) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

(32) D. J. Hupe and M. C. R. Kendall, unpublished.

(33) J. Hine, C. Y. Yeh, and F. C. Schmalstieg, *J. Org. Chem.*, **35**, 340 (1970).

(34) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **88**, 3367 (1966).

stants for imine formation than primary amines of comparable pK_a with sp^2- or sp-hybridized β carbons.

In summary, as the pK_a of the amine catalyst increases, k_A diminishes, k_{AB} remains constant, and k_B increases, until, when the pK_a becomes greater than 9, the general base term dominates the catalysis. For example, with 0.1 *M* total allylamine as catalyst at its pK_a (9.49), where the bimolecular catalysis would be greatest, if we assume $k_{AB} = 4 \times 10^{-3}$, then the k_B term would be 30 times greater than the k_{AB} term.

The question of whether secondary amines with pK_a's comparable to those of CMA, TFE, and EG would exhibit similar k_A and k_{AB} terms was not answered in the present study.[35] A search was made, however, using both primary and secondary amines with $pK_a > 9$ for terms other than k_{OH} or k_B. For certain amines (*e.g.*, pyrrolidine) the slopes of k_{obsd} *vs.* free amine concentration may have been slightly higher at pH values well below the pK_a (suggesting a term proportional to protonated amine), but this effect was so small as to be uncertain. In Bender and Williams' study of the enolization of acetone,[2] on the other hand, k_A terms with high-pK_a nontertiary amines were very important, representing positive deviations of up to 10^6 from the Brønsted line for general acid catalysis of enolization. They likewise ascribed this term to water-catalyzed deprotonation of intermediate iminium ions like **12**. This apparent discrepancy will be considered further below.

One might also expect a k_{AB} term in which the general base is hydroxide ion. This term would, of course, be kinetically indistinguishable from general base catalysis, as shown in eq 3. Only for relatively high pK_a amines, however, would $[RNH_3^+][OH^-]$ be large enough to make this term detectable. The small positive deviation for pyrrolidine from the secondary amine line in the Brønsted plot in Figure 2 may be an instance of operation of such a mechanism. Pyrrolidine, as previously noted,[15,36] has an especially favorable equilibrium constant for imine formation.

$$\frac{d[2]}{dt} = k_{AB}[RNH_3^+][OH^-][1] = k_{AB}\frac{K_w}{K_a}[RNH_2][1] = k'[RNH_2][1] \quad (3)$$

The observation of a distinct, dominant bimolecular k_{AB} term, as manifested in the bell-shaped curve in Figure 4 for cyanomethylamine, presented the opportunity for a more detailed study of this type of catalysis. Since general base catalysis of proton abstraction from an iminium ion formed between a carbonyl compound substrate and the ϵ-amino group of a lysine residue may be an integral part of the mechanism of several enzymic reactions,[11-13] such a study involves an unusually good biochemical model system.

One of the aspects of such a catalytic process which was readily amenable to investigation was determination of an approximate Brønsted β for proton abstraction from iminium ion **12**. To this end, several general bases were added to CMA solutions so that k_{AB} terms could be measured when the general base was something other than free CMA or water. Dimethylcyanomethylamine (DCMA), acetate ion, or imidazole added to CMA solutions produced pH–rate profiles (*e.g.*, Figure 5) having a new k_{AB} term with a maximum at a pK_a between that of CMA and the added general base. No measurable term was found for $k_{AB}[CMAH^+][B]$ when the base was hydroxide ion, as shown by the lack of positive deviation from the Brønsted plot for the k_B term of CMA. In Table III these k_{AB} values are summarized, including the k_{AB} term where water is the base, obtained by dividing k_A by 55 *M*. An upper limit was estimated for the case where the base is hydroxide ion by assuming that a maximum of one-half of the observed catalysis proportional to free amine occurs by this mechanism. The Brønsted plot of these data indicates that β is *ca.* 0.5, a value comparable to that (0.5) obtained by Hine[37] for general base catalyzed proton abstraction from an aldiminium ion.

The somewhat lower value of 0.4 for β found by Bender and Williams[2] for deprotonation of the iminium ion from glycine and acetone, indicating that water would be a relatively effective proton abstractor in that case, is consistent with their finding of significant k_A terms for high-pK_a amines. However, it is difficult to accommodate all of their data within the framework we have been proposing. Whereas we observe a decrease in the magnitude of the k_A term with increasing catalyst pK_a, Bender and Williams report large k_A terms which vary considerably and irregularly, but show, if anything, a tendency to increase with increasing catalyst pK_a. In a study of base-catalyzed elimination reactions of 4-benzoyloxy-2-butanones, Fedor[38] was unable to detect any covalent catalysis with primary amines having $pK_a > 9$, a finding consistent with our results.

There are several other incongruities in Bender and Williams' data[2] which are relevant to any attempt to analyze our own evidence completely. The values of k_{AB} which they list are, like ours, relatively independent of the pK_a of the catalyst, but it is not clear why they failed to report such terms for other similar primary amines studied. The β of 0.4 for α-proton abstraction from the glycine iminium ion differs markedly from the value of β of 0.75 which can be calculated from their values for the k_A and k_{AB} terms for *p*-toluidine. As will be discussed later, no evidence was found in this study of a k_A term for imidazole analogous to that reported.[2]

Another important aspect of covalent catalysis of this type is determination of the relative ease with which a given general base can abstract an α-proton from an iminium ion as compared to the parent carbonyl compound. Previous estimates of this rate enhancement range from Hine's[34] value of *ca.* 10^3 in the case of the methyliminium ion from isobutyraldehyde to Bender's[2] value of *ca.* 10^8 in the case of the methyliminium ion from acetone. It seems unlikely that such a large difference can be ascribed solely to the difference in carbonyl compound structure, so there is a clear need for further efforts to evaluate this ratio.

Such evaluations depend, of course, on measurement or estimation of the concentration of iminium ion. Wil-

(35) J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967), have found that covalent catalysis by secondary amines is unimportant in the α-exchange reaction of isobutyraldehyde.

(36) T. A. Spencer and L. D. Eisenhauer, *ibid.*, **35**, 2632 (1970); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(37) J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, *J. Org. Chem.*, **32**, 2205 (1969).

(38) R. C. Cavestri and L. R. Fedor, *J. Amer. Chem. Soc.*, **92**, 4610 (1970).

liams and Bender[30] report values of equilibrium constants for ketimine formation (K_e = [>C=NR]/[>C=O][RNH$_2$]) of *ca.* 0.1 M^{-1} for amines with pK_a > 8. This value would be expected to decrease slightly with decreasing catalyst pK_a,[33] as discussed earlier. If we then make the same assumption made by Bender[2] and Hine,[34] that $K_a^{imine} = 10^3 K_a^{amine}$, the amount of iminium ion in solution may be calculated. For example, in a 0.1 *M* CMA solution at its pK_a, the ratio [>C=N$^+$HR]/[>C=O] = K_e[RNH$_3^+$]K_a^{amine}/K_a^{imine} = (0.1)·(0.05)/10^3 = 5 × 10^{-6}. From the observed rate under these conditions for the k_{AB} term, 1 × 10^{-5} sec^{-1}, the bimolecular rate constant, k_2, for the reaction of iminium ion **12** with amine may be determined from k_2 = k_{obsd}/[>C=N$^+$HR][RNH$_2$] = 10^{-5}/(5 × 10^{-6})(0.05) = 40 M^{-1} sec^{-1}. Comparison of this value with the corresponding second-order rate constant for the reaction of **1** with cyanomethylamine, k_B = 4 × 10^{-5} M^{-1} sec^{-1}, indicates that conversion of **1** to the cyanomethyliminium ion has increased the rate of α-proton abstraction by the same general base by a factor of 10^6.

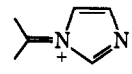
This value refers specifically to the iminium ion formed from **1** and CMA, which would be expected to be more susceptible to deprotonation than an iminium ion from a more basic amine, as discussed above. By analogy with the decrease in k_A with increasing catalyst pK_a (Table II), one can estimate the factor of 10^6 would decrease to *ca.* 10^3 for an amine with a pK_a of 9.5. Our evaluation thus is consistent, within the substantial uncertainties inherent in such estimations, with the 10^3 ratio reported by Hine[34] and the 2 × 10^4 enhancement reported by Lienhard[3] upon conversion of ethyl thioacetate to its dimethyliminium derivative. Our factor of 10^6–10^3, corresponding to a catalyst pK_a range of *ca.* 5–10, is not, however, in accord with the larger value of *ca.* 10^8 determined by Bender and Williams[2] on the basis of the large k_A terms they found with high-pK_a amines.

The temperature-dependence studies in the present work (Table V) also serve to illuminate the bimolecular catalysis as a model for enzymic processes. The k_{OH}·[OH$^-$] and k_B[(CH$_3$)$_3$N] terms are characterized by rather similar values of the activation parameters. There is surprisingly little information in the literature with which to compare these data on direct α-proton abstraction, but from rate data reported by Bothner-By and Sun,[39] values for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of 27.7 kcal/mole and −13 eu, respectively, for acetate ion catalyzed enolization of acetone can be calculated.

The k_{AB}[CMA][CMAH$^+$] term in the present work has a value of $\Delta G^{\ddagger}$ which is quite comparable to those for the k_{OH}[OH$^-$] and k_B[(CH$_3$)$_3$N] terms. It is, however, partitioned quite differently into enthalpy and entropy components, having a large negative $\Delta S^{\ddagger}$, as one would predict for the highly organized transition state between **12** and **13**, and a decidedly smaller $\Delta H^{\ddagger}$. This can be interpreted as an impressive illustration of the principle by which enzymes are believed to be able to catalyze reactions so effectively: lowering $\Delta G^{\ddagger}$ by utilizing a multifunctional catalytic system which can operate *via* a pathway with small $\Delta H^{\ddagger}$ and avoiding, by virtue of intramolecularity, the large $-T\Delta S^{\ddagger}$ term which characterizes a nonenzymic system such as the present model.

(39) A. A. Bothner-By and C. Sun, *J. Org. Chem.*, **32**, 492 (1967).

Finally, the catalytic role of imidazole bears further consideration. Our results with imidazole buffer do not support Bender's[2] apparent inference of catalysis of the enolization of acetone *via* iminium ion **15**. Bender and Williams[2] report a large (>10^3) positive deviation for imidazolium ion from the Brønsted line for general acid catalyzed enolization, which presumably, although not explicitly, they ascribe to catalysis involving the conversion of **15** to **16** as the rate-limiting step. Analogous intermediates have also been proposed by Lienhard and Wang[3] and by Kallen and Jencks.[40] In the present study, however, imidazole's behavior is exclusively that of an unhindered general base, and is almost exactly the same as that of *N*-methylimidazole. On the basis of this evidence and the inherent unfavorability of the formation of such species as **15**, in which the aromatic character of the imidazole ring[41] has been at least partially disrupted, we feel that the proposals of such species as intermediates in effective catalytic pathways should be very carefully scrutinized.[42]



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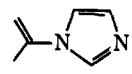


16

Experimental Section

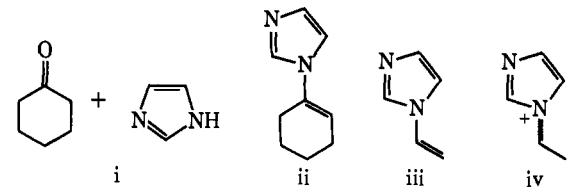
10-Methyl-Δ^{1,9}-octalone-2 (2). To a solution of 4.80 g (0.0265 mol) of 9-hydroxy-10-methyl-*cis*-decalone-2 (**3**), prepared by the method of Marshall and Fanta,[16] in 80 ml of methanol was added 25 ml of 20% aqueous potassium hydroxide solution. The mixture was heated on a steam bath for 10 min and then was extracted with ether. The extracts were combined, dried over sodium sulfate, and evaporated to afford an orange oil which was distilled to yield 2.05 g (71%) of **2**: bp 80–85° (0.5 mm) (lit.[16] bp 82–83°, 0.7 mm); uv max (H_2O) 247 mμ (ε 15,500); ir (film) 6.20 and 6.42 μ; nmr ($CDCl_3$) δ 1.21 (s, 3, H_3C), and 5.63 ppm (s, 1, HC=C).

10-Methyl-1,9-β-oxydecalone (4). In a modification of the procedure of Kuehne and Nelson,[17] a solution of 2.9 g (0.018 mol)

(40) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5851 (1966).

(41) The stabilization energy of the imidazole system is not accurately known; values ranging from 12 to 32 kcal/mol have been calculated; see, *e.g.*, H. Zimmermann and H. Geisenfelder, *Z. Elektrochem.*, **65**, 368 (1961).

(42) In unpublished experiments in this laboratory, B. F. Sweeney has gained confirmatory evidence that iminium ion formation between imidazole and carbonyl compounds is very difficult, and hence can be disregarded as a catalytic pathway. First, Sweeney has tried forcing conditions (*e.g.*, *p*-toluenesulfonic acid in refluxing toluene) in attempts to prepare and detect spectrally or isolate imidazole enamines (*e.g.*, ii from i) with no success. Second, he has demonstrated that the commercially available (Badische Anilin- & Soda-Fabrik AG) example of this type of enamine, *N*-vinylimidazole (iii), is *not* hydrolyzed under typical reaction conditions used in this study.[42a] This unusual stability



i ii iii iv

to hydrolysis also indicates that formation of species such as iv is energetically unfavorable and that they play no role in catalysis by imidazole. Since Bender and Williams[2] used disappearance of triiodide ion to follow the enolization reaction, Sweeney suggested that the "catalysis" reported may have been due to iodination of imidazole (*cf.*, J. H. Ridd, *J. Chem. Soc.*, 1238 (1955)), despite Bender and Williams' claim that a control run was made with each amine alone.

(42a) NOTE ADDED IN PROOF. Professor Konrad Bloch of Harvard University has informed us that M. Morisaki and he have isolated imidazole enamines formed by conjugate addition of histidines to 2,3-decadienoyl ethyl thioester. These imidazole enamines were stable to 6 *M* HCl or 10% NaOH at reflux temperature. We have recently found that *N*-vinylimidazole likewise is unaffected by being heated at reflux in 5 *M* HCl for 21 hr.

of enone **2** in 200 ml of methanol was cooled to 10° and treated with 15 ml of 30% aqueous hydrogen peroxide solution. To this mixture was added 4 ml (0.01 mol) of 20% aqueous sodium hydroxide solution dropwise over a 40-min period while the temperature was allowed to rise to 20°. The reaction was followed by tlc (on silica gel G using 2:3 ether–hexane with sulfuric acid spot development) and was complete after 60 min. The basic reaction mixture was diluted with an equal volume of water and extracted with four 20-ml portions of ether. The ether extracts were combined, washed with dilute sodium hydroxide solution, dried over sodium sulfate, and evaporated to afford 2.81 g of clear oil. The original reaction mixture was acidified with hydrochloric acid and was extracted with two 20-ml portions of ether. These extracts were dried over sodium sulfate and evaporated to yield 0.442 g of an unidentified acidic product. The 2.81 g of neutral product was a 7:3 mixture of **4** and the isomeric α-oxide, as indicated by the nmr methyl peaks at δ 1.17 and 1.03, respectively. The pure β isomer was obtained by dissolving the mixture in an equivalent volume of hexane and placing it in the freezer for 24 hr, whereupon colorless crystals were obtained. Recrystallization from hexane yielded 1.10 g (35%) of **4**: mp 56–57° (lit.[17] mp 58–60°); ir (KBr) 5.86 and 11.77 μ; nmr ($CDCl_3$) δ 1.17 (s, 3, H_3C) and 2.80 ppm (s, 1, C_1H).

2,9-Dihydroxy-10-methyl-*cis*-decalins 5 and 6. To a slurry of 0.94 g (0.025 mol) of lithium aluminum hydride in 200 ml of dry ether was added a solution of 2.0 g (0.011 mol) of **4** in 50 ml of dry ether dropwise at room temperature. The resulting mixture was refluxed for 1 hr and was stirred for 2 hr at room temperature. It was then cooled to 0°, and 1 ml of water, 0.5 ml of 20% aqueous sodium hydroxide solution, and another 3 ml of water were added dropwise. The white precipitate which had formed was filtered with the aid of Celite and the clear ethereal filtrate was dried over sodium sulfate. The solvent was evaporated to afford 2.03 g (99%) of a crude mixture of diols **5** and **6**: ir (KBr) 2.80 μ.

2,9-Diacetoxy-10-methyl-*cis*-decalins 7 and 8. A solution of 2.03 g (0.0110 mol) of the crude mixture of diols **5** and **6** in 25 ml of isopropenyl acetate containing a crystal of *p*-toluenesulfonic acid was refluxed for 36 hr. The reaction mixture was cooled, washed with two 10-ml portions of 5% aqueous sodium bicarbonate solution, dried over sodium sulfate, and evaporated to afford 2.70 g (95%) of a mixture of **7** and **8**: ir (film) 5.80 μ; nmr (CCl_4) δ 1.00 and 1.05 (2 s, H_3C) and 1.90 and 2.00 ppm (2 s, H_3CCOO).

2-Hydroxy-9-acetoxy-10-methyl-*cis*-decalins 9 and 10. To a solution of the 2.70 g (0.0104 mol) of the crude mixture of diacetates **7** and **8** in 50 ml of methanol was added 0.5 ml of 50% sodium hydroxide solution at room temperature. The disappearance of **7** and **8** was followed by tlc on silica gel G, using 2:3 ether–hexane with sulfuric acid spot development. After 35 min the starting material was almost gone and the main products were **9** and **10**. The mixture was diluted with 150 ml of water and was extracted with three 25-ml portions of ether. The extracts were combined, dried over sodium sulfate, and evaporated to yield 2.04 g of yellow oil. Separation of **9** and **10** from this mixture was accomplished by preparatory tlc on 1.3-mm thick plates of silica gel PF using 3:2 ether–hexane. In a typical separation, 0.100 g of the reaction product was chromatographed to afford 0.060 g of a clear, oily mixture of **9** and **10**, which showed one spot on tlc: ir (film) 2.95 and 5.80 μ; nmr ($CDCl_3$) δ 1.00 and 1.04 (2 s, H_3C) and δ 1.94 and 1.98 ppm (2 s, H_3CCOO).

9-Acetoxy-10-methyl-*cis*-decalone-2 (1). To a solution of 0.225 g (0.99 mmol) of **9** and **10** in 25 ml of reagent grade acetone cooled to 0° was added 0.5 ml (4.0 mmol) of 8 *N* Jones reagent.[19] After 3 min the reaction mixture was poured into a separatory funnel containing 75 ml of water and the resulting solution was immediately extracted thoroughly with methylene chloride. The extracts were dried over sodium sulfate and the solvent was evaporated to yield an oil which was dissolved in 2 ml of hexane and cooled in a Dry Ice–acetone bath. Colorless crystals formed, which were collected and recrystallized from hexane to yield 0.195 g (88%) of **1**: mp 49–50°; ir (KBr) 5.82 μ; nmr ($CDCl_3$) δ 1.17 (s, 3, H_3C), 1.97 (s, 3, H_3CCOO) and 2.04 ppm (AB quartet, J = 14 Hz, 2, O=CCH_2C).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.62; H, 9.03.

Preparation of Deuterium-Labeled Substrate (1-C_1-d_2). To a solution of *ca.* 1 g of sodium metal in 80 ml of deuteriomethanol, prepared by the method of Streitwieser,[43] was added 24.0 g (0.043 mol) of enone **2**. The mixture was stirred at room temperature for 24 hr and then most of the solvent was removed by distillation. The residue was dissolved in ether, which was extracted with four 5-ml portions of deuterium oxide, dried over sodium sulfate, and evaporated to yield a yellow oil. Integration of the nmr spectrum of this oil indicated that about 80% of the vinyl proton signal at δ 5.63 ppm ($CDCl_3$) has disappeared. The above exchange procedure was repeated twice for 36 hr each, producing material with estimated 93% and 99% deuterium incorporation at C_1, respectively. Distillation [80–85° (0.5 mm)] of this material afforded 17.0 g (70%) of **2**-C_1-d_1: uv max (H_2O) 247 mμ (ϵ 15,500); ir (film) 4.65, 6.00, and 6.22 μ; nmr ($CDCl_3$) δ 1.21 ppm (s, 3, H_3C).

All the steps for the conversion of this labeled **2** to **1**-C_1-d_2 were carried out by exactly the same procedures described above for unlabeled material except the final oxidation with Jones reagent, which was allowed to proceed at 15–20° for 10 min with the deuterated hydroxyacetates. Nmr spectra of the various intermediate products indicated that negligible loss of label at C_1 occurred throughout the sequence, and the absence of any detectable AB quartet resonance for C_1 protons in the nmr spectrum of the labeled ketoacetate confirmed that it was **1**-C_1-d_2. The nmr spectrum of the intermediate epoxide **4**-C_1-d_1 did indicate, however, that some exchange at C_3 occurred during epoxidation of **2**-d_5. This conclusion was confirmed by the mass spectrum of the **1**-C_1-d_2 obtained, which indicated that it was a mixture of d_4, d_5, and d_6 species.

Other Materials. Liquid amines used in these experiments were purified either by two recrystallization of the hydrochloride from 1:1 methanol–1-propanol, or by distillation twice from barium oxide directly before use. The solid amines imidazole, piperazine and 1,4-diazabicyclo[2.2.2]octane were purified by recrystallization twice from ether.

Apparatus. A Unicam SP 800B spectrophotometer equipped with an automatic cell changer timed by a Cary 1116100 program timer was used to obtain data for four kinetic runs simultaneously. The temperature in the cuvettes was maintained at 25.0 ± 0.1° by circulating water controlled by a P.V. Tamson bath through the cuvette housing. Ultraviolet scans were made using a Cary 14 spectrophotometer. pH measurements were made on a Radiometer Model 26 pH meter equipped with a GK2302C combination electrode.

Kinetics. The course of the reaction of **1** was monitored by measuring the uv absorbance of the product **2** at 247 mμ. The absorbance of the starting material at this wavelength was negligible and whatever small amount of absorbance was due to catalyst was balanced by an equivalent concentration in the blank cuvette. All runs were carried out under pseudo-first-order conditions. Substrate concentration varied from 5×10^{-5} to 2×10^{-3} *M* and the consistency of results over this range confirms the validity of the assumption of first-order dependence on substrate. The ionic strength was maintained at μ = 0.4 with potassium chloride except in those few instances when the concentration of ionic catalysts made the value somewhat larger. In order to measure k_{obsd} as a function of catalyst buffer concentration at one pH, a procedure was employed yielding four data points simultaneously. A measured amount of purified amine or its hydrochloride was dissolved in water and adjusted to the desired pH with hydrochloric acid or potassium hydroxide solution, and enough potassium chloride was added so that the ionic strength was 0.8 after the solution was diluted to volume. By using a syringe fitted with a Chaney adapter, precisely measured volumes of the amine stock solution could be diluted with 0.8 *M* potassium chloride solution so as to produce a series of amine solutions all having about the same pH and μ, but with concentration ratios of 1:0.67:0.50:0.33. At the start of the reaction each of these solutions was rapidly mixed in the cuvette with an equal volume of an aqueous solution of **1** at twice the desired final concentration, whereas the blank in each case was made with water and the amine solution. Absorbance readings were taken at intervals ranging from 1 min to several hours depending on the half-life under the conditions employed. Reactions were routinely followed for several half-lives and gave good linear pseudo-first-order plots. However, when the conditions employed produced **2** at an inconveniently slow rate, a relatively high concentration of **1** was used and only the first few per cent of reaction was studied. This technique was used with CMA as catalyst also to avoid complications encountered with long-standing aqueous CMA solutions, presumably as a result of decomposition of the catalyst to ammonia, formaldehyde, and hydrogen cyanide.

Absorbance at zero time (A_0) was obtained by extrapolation of initial readings to zero time. The infinity absorbance was either calculated from the weight of starting material or measured on an aliquot of substrate which was diluted to a known volume with di-

(43) A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

lute sodium hydroxide solution in order to complete formation of 2. Good agreement was obtained when both methods were used.

The value of k_{obsd} for each run was obtained from the slope of $\ln(1/[1 - (A_t - A_0)/(A_\infty - A_0)])$ *vs.* time in seconds, and could be determined either graphically or by a least-squares fit of the data points by computer. The values of k_{obsd} for a series of buffer dilutions, when used to obtain a second order rate constant by plotting *vs.* catalyst concentration, were first corrected for minor differences in hydroxide ion concentration. Choosing the hydroxide ion concentration of the most concentrated buffer as the reference, $[OH^-]_{ref}$, the values of k_{obsd} for series were then corrected according to the expression

$$k_{obsd\ corr} = k_{obsd\ uncorr} + k_{OH}([OH^-]_{ref} - [OH^-]_{obsd})$$

The values listed as k_{obsd} throughout this paper are values of $k_{obsd\ corr}$. Temperature dependence measurements were conducted by use of the constant temperature water circulator at 20, 25, 30, and 35° and plots of $\ln k$ *vs.* $1/T(°K)$ showed good linearity and yielded a slope of $-E_a/R$. The other activation parameters were calculated as indicated in Table V. The values of k_{AB} at each temperature were obtained from the slope of the linear portion of a plot of k_{obsd} *vs.* [CMA][CMAH$^+$]. The value obtained at 25° by this method was identical with that obtained by first subtracting k_B and k_A terms as described in the Results section.

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The Mechanism of the Acid-Catalyzed Hydrolysis of Methyl Thiolformate

Robert Hershfield[1] and Gaston L. Schmir*

Contribution from the Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, Connecticut 06510.
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Abstract: The pH–rate profile for the hydrolysis of methyl thiolformate in H_2O (30°) has been determined in the pH range 0–4.6. The dependence of the reaction rate on acidity has been interpreted in terms of a mechanism involving the participation of cationic and neutral tetrahedral addition intermediates, with a change in rate-determining step occurring at pH 1.2. In a parallel study, the hydrolysis of the ketene *O,S*-acetal I has been found to be subject to catalysis by hydronium ion and acetic acid. The products of the reaction vary with pH, the predominant product at acid pH being the thiol ester III, while mainly the oxygen ester IV is formed at pH > 3. The observation that the effect of pH on the rate of the reaction does not parallel its influence on the nature of the reaction products supports the postulation of at least one intermediate on the reaction pathway. The properties of the related intermediates formed in the hydrolyses of methyl thiolformate and of I have been compared and found to be in general agreement.

Kinetic studies of the hydrolysis of thiol esters were reported at least as early as 1948,[2] and continued sporadically for the next decade.[3] The first evidence for the formation of tetrahedral addition intermediates in thiol ester hydrolysis was described by Fedor and Bruice in their important investigation of the hydrolysis of ethyl trifluorothiolacetate;[4] their conclusions, based on kinetic arguments, were later confirmed by oxygen exchange experiments.[5] So far as we are aware, direct evidence for tetrahedral intermediates exists only for thiol esters derived from trifluoroacetic acid.[4-6]

The present investigation of the hydrolysis of methyl thiolformate was undertaken to establish whether tetrahedral intermediates could be shown to be a general feature of thiol ester hydrolysis. If this were the case, we were interested in obtaining information concerning the possible existence of various ionic forms of the intermediates, and in determining the pathways of breakdown of each species.

The generation of the intermediates of acyl transfer reactions by indirect routes which do not lie on the main reaction path for acyl transfer has provided a useful ancillary approach to the study of the properties of these transient intermediates.[7] For instance, the assignment of the nature of the rate-limiting steps under various conditions in the aminolysis of esters and in the alcoholysis of amides was facilitated by parallel studies of the hydrolysis of imidate esters.[8-11] With regard to

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